MEMORANDUM

SUBJECT: **DICHLORVOS (DDVP): According to the Registrant: Critical Studies on Dichlorvos which Must be Evaluated for the EPA HED RED.**

EPA DP Barcode: D255121
EPA Submission Barcode: S560054
EPA Pesticide Chemical Code 084001

FROM: Ghazi Dannan, Ph.D.
Pharmacologist

and

Stephen C. Dapson, Ph.D.
Branch Senior Scientist
Registration Action Branch 3/HED (7509C)

THRU: K.Clark Swentzel
Branch Chief
Registration Action Branch 3/HED (7509C)

TO: Susan Hummel
Branch Senior Scientist
Reregistration Action Branch 4/HED (7509C)

Registrant: AMVAC

Action Requested: Determine if the studies provided have been reviewed before and critically review those studies which have not been reviewed; for DDVP.

Recommendations: RAB3 evaluated the open literature and contracted studies submitted by the registrant. These studies were, for the most part, open literature studies that were published more than 30 years ago, had no supporting data to verify the toxicity endpoints, and were not designed for dose-response assessment. While a variety of species (including man) were tested, none of the submitted studies had a comparative assessment of man to other species, and most human studies lacked the essential quantitative exposure and toxicity assessments needed to quantify and characterize the risk. Further, AMVAC did not provide an accompanying report that specifies their position based on a comprehensive assessment of the studies they provided and other

existing published data on DDVP. Henceforth, it was difficult for RAB3 reviewers to determine the exact significance or relevance of the provided studies towards EPA's Preliminary Risk Assessment of DDVP. Nonetheless, and after a thorough evaluation of the submitted studies, RAB3 has reached the following conclusions.

The studies do not add any new information to the relevant database for animal studies with DDVP; however, they suggest (but do not prove) that humans might **not** be more sensitive by the inhalation route of exposure to DDVP vapors than the animal models (see study citations #7, 9, 10, 11, 14 and 19 for relevant human exposure information). The current inhalation risk assessment for DDVP was based on a two-year rat inhalation study (MRID No. 0057695, 00632569) where NOAEL was 0.00005 mg/L based on plasma, RBC, and brain ChE inhibition at the next higher dose of 0.00048 mg/L (HIARC reports dated 12/19/97 and 6/3/98 HED Document No. 012448 and 12629). For the short-term inhalation exposure risk assessment in humans, this NOAEL value seems to be too conservative, especially after adding the 10-fold uncertainty factor (UF) for intra-species variability. The Arizona III human study, with repeated measurements of air concentrations of DDVP and of plasma and RBC ChE levels, might be a more suitable study for the short-term (one month or less) inhalation exposure risk assessment. In this study, where residents spent nearly 50% of their time inside the house, the actual NOEL for human plasma and RBC ChE inhibition seems to be in the range of 0.0001 mg/L (0.1 mg/m^3) which is an average home air concentration from hanging one 20% DDVP resin strip/1000 cubic feet/month (citation 11, also reviewed by J. Stewart and H. Spencer on 4/8/93, HED Document no. 010157). Based on this study, and after accounting for the average time spent (~ 50%) at home, the NOEL in humans would be approximately equal to the NOAEL in the two-year rat inhalation study (0.00005 mg/L). RAB3 recommends using the NOEL from the Arizona III study for the short-term risk assessment, thereby, obviating the need for the 10-fold UF for intraspecies extrapolation. RAB3 has reached this conclusion despite the fact that the study was classified **core-Supplementary** because "as a journal article it was not presented in enough detail for complete assessment of the information to be made, although it provides valuable information" (J. Stewart and H. Spencer, HED Document no. 010157 dated 4/8/93).

On the other hand, RAB3 agrees with the HIARC conclusions that the two-year rat inhalation study (MRID No. 0057695, 00632569) is the most suitable study available for the intermediate- and long-term inhalation risk assessments. Nonetheless, if the MOEs from the risk assessment for DDVP are marginally acceptable, RAB3 suggests that the risk assessor can inform the risk manager that the animal numbers can be used with the idea that the human might not be more sensitive by inhalation exposure to DDVP vapors than the animal models.

The following are specific comments by RAB3 on the submitted open literature studies:

Human and Animal Health Studies

Studies that are critical to an estimate of the inhaled dose to rats in the chronic inhalation rat study by Blair et al.

1. CITATION: Stevenson, D.E., and D. Blair. (1977). The uptake of dichlorvos during long-term inhalation studies. Proc. Eur. Soc. Toxicol. 18: 215-217.

EPA Comment: This study contains some minor pharmacokinetic and metabolism discussion, does not contain any useful data.

2. CITATION: Cochran, R.C., T.A. Formoli, K.F. Pfeifer, and C.N. Aldous. (1997). Characterization of risks associated with the use of molinate. Reg. Tox. & Pharm. 25:146-157.

EPA Comment: This study discusses Molinate and does not add to DDVP database.

Studies that determine the effects of single/repeated exposures of dichlorvos via inhalation.

3. CITATION: Durham, W.F., T.B. Gaines, R.H. McCauley, Jr., V.A. Sedlak, A.M. Mattson, and W.J. Hayes, Jr. (1957). Studies on the toxicity of 0,0-dimethyl-2,2-dichlorovinyl phosphate (DDVP). Am. Med. Assoc. Arch. Ind. Health 15: 340-349.

Study Summary: The acute oral and dermal LD_{50} values of DDVP for male white rats were found to be 80 and 107 mg/kg, respectively. The corresponding values for females were 56 and 75 mg/kg. Pure DDVP was found, under the conditions studied, to be somewhat more toxic than the technical material.

Feeding for 90 days at dietary levels of DDVP up to 1000 ppm caused no signs of intoxication in rats. However, dietary levels as low as 50 ppm produced definite lowering of plasma and erythrocyte cholinesterase levels.

Three monkeys were killed by, 8, 10 and 4 doses, respectively, of DDVP given dermally at the respective rates of 50, 75, and 100 mg/kg.

Monkeys confined for two weeks in Peet-Grady chambers which had been sprayed with 100 and 195 mg. of DDVP per square foot showed depletion of both plasma and erythrocyte cholinesterase. The concentration of DDVP in the air-of the chambers sprayed at the rate of 195 mg/sq.ft. varied from about 6 gamma (micrograms) per liter immediately after spraying to 0.1 gamma per liter at the end of two weeks. Rats under the same condition showed a less definite enzyme inhibition. Neither species showed any clinical signs of organophosphorus intoxication.

Confinement in a Hazleton-type respiratory chamber, in which their entire air supply was essentially saturated with DDVP, proved fatal to rats in 4.8 to 83.0 hours, depending on

conditions. The concentration of DDVP vapor exceeded 30 gamma per liter.

Some laboratory personnel constantly working with DDVP experienced an unpleasant metallic aftertaste as a result of their exposure. The four most severely exposed workers showed a small but definite decrease in erythrocyte cholinesterase level.

A screening test using chickens gave no indication of a neurotoxic effect resulting from severe DDVP exposure.

DDVP was found to be a potent cholinesterase inhibitor in vitro.

EPA Comment: There was equivocal effects on plasma cholinesterase and decreased red blood cell cholinesterase with no clinical signs of OP exposure.

4. CITATION: Foll, C.V., C.P. Pant, and P.E. Lietaert. (1965). A large-scale field trial with dichlorvos as a residual fumigant insecticide in northern Nigeria. Bull. World Health Organ. 32:531-550.

EPA Comment: No useful toxicology information.

5. CITATION: Funckes, A.J., S. Miller, and W. Hayes (1963). Initial field studies in Upper Volta with dichlorvos residual fumigant as a malaria eradication technique. Bull. Org. Mond. Sante Bull. Wld. Hlth Org.. 29:243-246.

EPA Comment: Need more information on type of house, no useful toxicology information.

6. CITATION: Gratz, N. G., P. Bracha, and A. Carmichael. (1963). A village - scale trial with dichlorvos as a residual fumigant insecticide in southern Nigeria. Bull. Org. mond Sante Bull. Wld. Hlth Org. 29:251-270.

EPA Comment: No useful toxicology information.

7. CITATION: Hayes, W. J. (1961). Safety of DDVP for the disinsection of aircraft. Bull. Org. mond. Sante Bull. Wld. Hlth Org. 24:629-633.

Study Abstract: DDVP (O,O-dimethyl-2,2-dichlorovinyl phosphate) is an organic phosphorus insecticide proposed for the disinsection of aircraft at vapour concentrations within the range of 0.15-0.25 μg per litre of air for 30 minutes. Safety tests have shown that men can withstand brief exposure to concentrations as high as 6.9 μg per litre and daily 8-hour to concentrations as high

as 0.5 μg per litre without clinical effect and with little or no depression of blood cholinesterase. It would appear, therefore, that DDVP could be safely used at the concentrations and exposure periods required for the disinsection of aircraft, though further studies will have to be carried out before this procedure can be definitely recommended.

EPA Comment: Study used closed system, slight decrease in ChE, no clinical signs noted. The apparent NOAEL for inhalation exposure is approximately 0.5 μg/L for an 8 hour exposure period.

8. CITATION: Hunter, C.G. (1969). Dichlorvos: Human Inhalation Studies. Shell Research Limited, Sittingbourne, Kent, England.

Abstract: Human inhalation exposures to the vapor of dichlorvos, an anticholinesterase insecticide, have been made to define dose-response relationships at concentrations of the order of the TLV and above. The clinical and laboratory observations before, during, and after partial and total body exposures remained unaffected, except for alterations in the activities of plasma acetylcholinesterases. These were reduced, and the degree of reduction was directly related to the intensity of the exposure, concentration of dichlorvos vapor inhaled and the time of exposure in minutes. For any defined exposure the amount of reduction or inhibition of the enzyme system may be estimated.

EPA Comment: This is an **abstract**, not useful, need a full detailed article.

9. CITATION: Hunter, C.G. (1970). Dichlorvos: Inhalational exposure with human subjects. Part 1 (TLGR.0061.70) and Part 2 (TLGR.0067.70). Shell Research Limited, Sittingbourne, Kent, England.

Study Conclusions:

Part 1

1. Symptomatology was confined to the "detection" of the vapour of dichlorvos. There were no clinical signs of the exposures, the many observations made not departing from pre-exposure values.

2. No real changes occurred in the values of the activities of the erythrocyte acetylcholinesterases during exposures lasting up to 7.5 hours and repeated daily for 4 days. The activities of the plasma acetylcholinesterases were reduced with exposures, but continuous exposures of 6.5 - 7.5 hours are required to reduce the activities of this enzyme system to values significantly different from the pre-exposure ones.

3. A direct relationship exists between the exposure, concentration/time, and the activity of the plasma acetylcholinesterases and providing, the concentrations of the vapour of dichlorvos in the range of the TLV 1 mg/m^3 and the pre-exposure values of the plasma enzyme, are known the durations of exposures acceptable by individual workmen may be assessed.

4. No changes occurred in the values of the tests used to assess the functions of the lungs and kidneys.

Part 2

1. Symptomology was confined to irritation of the throats some rhinorrhea and subdermal discomfort at the highest concentrations. No effects on the pupil nor visual acuity were recorded.

2. In subject only the activities of erythrocyte acetylcholinesterases were slightly reduced - when exposures were greater than 1,450 mg/min/m^3.

3. The activities of plasma acetylcholinesterases were directly affected by the exposure and a relationship between reduction of activity and dose, concentration/time, exists when measurements are made immediately and 16-20 hours after exposures.

4. No changes were found in the observations made on kidney and pulmonary functions and rates of overall metabolism.

EPA Comment: Effects on cholinesterase only at extremely high dose levels (1,450 mg/min/m^3). ChE activities were determined before and after exposure. The authors felt that a TLV of 1

mg/m^3 was acceptable exposure.

10. CITATION: The Kettering Laboratory. (1965). Evaluation of Safety in the Use of Vapona Insecticide Resin Vaporizers. University of Cincinnati, June, 1965.

Study Discussion: The control of insects by means of the continuous vaporization of dichlorvos within enclosed spaces, in which persons are housed intermittently or continuously, provides the potential threat of the absorption of significant quantities of the material dispersed as vapor in the air. Despite the extensive toxicological investigation of dichlorvos, which has included observations of human beings (4, 5, 6, 8, 11, 12), no work had been done to evaluate the hazard of Vapona (R) Resin Vaporizers under the actual conditions of use. The observations described in this report were designed to reveal the significance, if any, of such hazards.

Handling the Vaporizers does not appear to cause any significant decrease in cholinesterase activity among those doing the handling, nor is the cholinesterase activity affected by the prolonged contact of the vaporizers with the skin of the forearm. In the ordinary day's work, the householder or the pest control operator would not be expected to handle the vaporizer as much as 30 minutes each day even under the most unusual conditions. Under ordinary circumstances, the contact of the resin vaporizer with the skin would not persist for 30 minutes, in any one day, and would not be continued day after day.

The exposure to Vapona(R) Resin Vaporizers in the general environment poses a somewhat different problem. Here, the potential hazard involves the combined effects of the absorption of the material through inhalation, through the skin, and from the alimentary tract (if swallowed). The observations made on 2 families over the period of 6 months, and of 6 other families over the period of 2 months, were designed to determine whether any adverse effect could be demonstrated.

The inhibition of the cholinesterase activity of the blood is the most sensitive means now available, with the possible exception of the inhibition of the esterase activity of the liver, for detecting the absorption of an organic phosphorus compound that is known to be capable of inducing this effect. The values indicative of cholinesterase activity are shown in Tables 3, 5, and 6. All subjects were exposed to the recommended dosage (one Vaporizer per 1000 cubic feet) except subjects 15 and 16, who were exposed to resin strips that did not contain any dichlorvos.

The data obtained were examined initially by plotting the cholinesterase activity of the erythrocytes and plasma against the day of exposure of each individual subject, and by summarizing the results obtained from each of the 3 test groups. These graphs revealed no consistent trend in any of the groups. The data were examined more closely for possible trends by fitting linear equations to each of the groups. In all three cases it was seen that the slope of the best equation, determined by the method of least squares, was not significantly different from

zero, indicating that the variations in the cholinesterase activity of the erythrocytes and plasma were not a function of the duration of the exposure of the subjects.

Dichlorvos is a known inhibitor of cholinesterase, and it is likely that under certain conditions of use a significant degree of such inhibition might occur. However, under the conditions of these experiments, no such effect appears to have occurred. The subjects yielded no indication of adverse effects.

It may be worth noting that, in addition to the human residents, two dogs and three cats were residents of the homes. None of the animals exhibited any difficulty during the period of exposure.

In these experiments the vaporizers were replaced at much shorter intervals than those normally recommended. Moreover in one instance, the vaporizers were employed continuously, in the presence of the subject, for a full week.

Conclusion: The handling and use of Vapona (R) Resin Vaporizers, under the recommended conditions, is unlikely to result in adverse effects among persons so exposed. ChE activities were determined 24 hours after exposure both in the handling group and those with the strip attached to the forearm.

EPA Comment: There were no significant effects at normal exposure.

11. CITATION: Leary, J.S., W.T. Keane, C. Fontenot, E.F. Feichmeir, D. Schultz, B.A. Koos, L. Hirsch, E.M. Lavor, C.C. Roan, and C.H. Hine. (1974). Safety evaluation in the home of polyvinyl chloride resin strip containing dichlorvos (DDVP). Arch Environ. Health 29:308-314.

Study Abstract: In a period of two years a series of three-home studies involving 26 families in Arizona was conducted to further evaluate the safety of the dichlorvos (DDVP)containing Insecticide strip. Physical examination, hematologic and clinical chemistry measurements, blood cholinesterase assays, and analysis of air and food for dichlorvos were carried out. Exposures were designed to be exaggerated in that strips were used throughout the homes (averaging 7 to 11 per home) and replaced with fresh ones, either every three months for one year or monthly for six months.

Throughout the studies, all examinations and measurements revealed no adverse effect on health. The red cell cholinesterase activity also remained unaffected. A slight plasma cholinesterase depression of no toxicological importance was observed In the study where the strips were replaced monthly over six months.

In homes containing 8 to 18 strips, maximum air and food concentrations of dichlorvos averaged approximately 0.13 mg/cu m and 0.12 ppm, respectively.

EPA Comment: This study was reviewed by the Agency on 4/8/93 (J. Steward, HED Document No. 010157). There were no significant findings at normal exposure levels; very slight decreases in plasma ChE.

12. CITATION: Mathis, W., A. St. Cloud, M. Eyraud, S. Miller, and J. Hamon. (1963). Initial field studies in Upper Volta with dichlorvos residual fumigant as a malaria eradication technique. 2. Entomological evaluation. Bull. Org. mond Sante (Bull. Wld Hlth Org.) 29:237-241.

EPA Comment: Not useful, need more information on home structure.

13. CITATION: Quaterman, K.D., M. Lotte, and H.P. Schoof (1963). Initial field studies in Upper Volta with dichlorvos residual fumigant as a malaria eradication technique. 1. General considerations. Bull Wld Hlth Org. 29:231-235.

EPA Comment: Not useful, need more information on home structure.

14. CITATION: Rasmussen, W.A., J.A. Jensen, W.J. Stein, and W.J. Hayes. (1963). Toxicological studies of DDVP for disinsection. of aircraft. Aerospace Medicine (July);593-600

Study Abstract: DDVP (O,O-dimethyl-2,2-dichlorovinyl phosphate) has been proposed for the disinsection of aircraft on international flights. It appears well adapted to this application since it

is possible to produce the desirable air concentrations of 0.15 to 0.25 μg of DDVP per liter of air for 30 minutes with little variation. This is an adequate level for killing of flies and mosquitoes, whereas men have withstood exposure to concentrations as high as 6.9 μg of DDVP per liter of air for 30 to 60 minutes without change of cholinesterase or noticeable clinical effect.

A study was made to determine the possible physiological effects of frequent exposures to DDVP on aircraft crews. Such exposures would be incurred by crews on certain airline routes, particularly in Central America and Africa. While it has been established that a few exposures to concentrations of DDVP far greater than those required for the disinsection of aircraft produce no signs or symptoms of poisoning in man, the obvious hazards of even temporary changes in visual functions, speed of reaction, or respiratory functions of crew members warranted further study. Because DDVP inhibits cholinesterase, measurements of this enzyme formed an important part of the study.

EPA Comment: This was a closed system, no ChE changes occurred until very high dose levels were achieved.

15. CITATION: Stein, W.J., S. Miller, and L.E. Fetzer, Jr. (1966). Studies with dichlorvos residual fumigant as a malaria eradication technique in Haiti. III. Toxicological studies. Am. J trop. Med. Hyg. 15(5):672-675.

EPA Comment: Not relevant to U.S. applications.

16. CITATION: Stevenson, D.E. and D. Blair. (1969). A Preliminary Report on the Inhalation Toxicity of High Concentrations of Dichlorvos. TLGR.0024.69. May, 1969.

Study Conclusions: The short term inhalation exposure tests showed differences in the susceptibility of the three species used, with mice most affected, and guinea-pigs least affected by exposure to dichlorvos atmospheres. Approximate no-visual-effect levels for five daily exposures of seven hours each were: 130 μg/litre for guinea-pigs and 50 pg/litre for rats and mice. Mice survived a single exposure to 130 μg/litre DCA for 5-7 hours.

EPA Comment: No ChE measurement were taken, only clinical signs were monitored with no effects noted.

17. CITATION: Ueda, K., and M. Nishimura. (1967). Effect of Vaponal Strips to Human Beings.

EPA Comment: Unknown if published, looks like personal communication or at least an abstract

of sorts. Human monitoring, no relevant effects noted.

18. CITATION: Walker, A.I.T., D. Blair, D.E. Stevenson, and P.L. Chambers. (1972). An inhalation toxicity study with dichlorvos. Arch Toxicol. 30:1-7.

Study Abstract: Dogs, cats and rabbits were continuously exposed for eight weeks to dichlorvos atmospheres generated from impregnated polyvinyl chloride strips. Concentrations of dichlorvos in air were produced in the range 0.05 to 0.3 μg/l. No effects were found on the general health, behaviour, plasma and erythrocyte cholinesterase activities and electroencephalographic patterns of the animals.

EPA Comment: No effects were noted in this study on plasma or RBC ChE levels, clinical signs and on ECGs.

19. CITATION: Witter, R. F., T.B. Gaines, J.G. Short, V.A. Sedlak, and DA. Maddock. (1961). Studies on the safety of DDVP for the disinsection of commercial aircraft. Bull World Health Organ. 24:635-642.

Study Abstract: There is a need for a more effective method for the disinsection of intercontinental aircraft. A study was made of the possible toxic hazard associated with a new method of disinsection using DDVP vapour (0,0-dimethyl-2,2-dichlorovinyl phosphate) as the insecticidal agent. In these experiments, men and monkeys were exposed four times over one- or two- hour periods for a total of 4-8 hours to DDVP vapour in a simulated aircraft cabin. The concentration of DDVP was higher and the exposure periods were longer than those planned for use in disinsection. Concentrations up to 0.7 μg per litre of air produced no effect on the cholinesterase of men or monkeys. It was found that a concentration of DDVP of 0.9-3.5 μg per litre of air caused a slight decrease in plasma cholinesterase of the men and the monkeys. At a DDVP concentration of 7.5- 17.9 μg per litre, monkeys exhibited a marked drop in red cell and plasma cholinesterase and showed miosis, but no other signs of poisoning.

EPA Comment: This was a closed system. They only saw effects on ChE at very high dose levels.

<u>Studies that determine the effects of single/repeated exposures of dichlorvos via ingestion.</u>

20. CITATION: Boyer A.C., L.J. Brown, M.B. Slomka, and C.H. Hine. (1977). Inhibition of human plasma cholinesterase by ingested dichlorvos: effect of formulation vehicle. Toxicol. APPL Pharm. 41:389-394.

Study Abstract: Human subjects were fed 0.9 mg of dichlorvos (2,2-dichlorovinyl dimethyl phosphate) three times a day for 21 days. No consistent cholinomimetic signs or symptoms were observed, nor was erythrocyte acetylcholinesterase inhibited. The only significant observation was a depression of plasma cholinesterase (ChE) activity. The magnitude of the depression in plasma cholinesterase was found to depend on the method by which dichlorvos was incorporated into the diet. Dichlorvos, formulated as a gelatin salad and consumed during the course of the meal was only 64% as effective in inhibiting ChE activity as when administered as a premeal capsule containing cottonseed oil. The recovery of cholinesterase activity, after dosing was terminated, was due to the replacement of the enzyme molecules. The half life for this regeneration period was 13.7 days.

EPA Comment: This study used the oral route.

21. CITATION: Rider, J.A. (1967). Determination of the Minimal Incipient Toxicity of Dichlorvos in Humans. Shell Chemical Company, October, 1967.

Study Conclusions:

1. According to our definition of the minimal incipient toxicity level which is that amount of the compound which, when ingested daily over a period of several weeks by humans, will produce a depression of plasma or RBC cholinesterase activity of 20 to 25% from control levels, the level of minimal incipient toxicity of dichlorvos appears to be between 1.5 and 2.0 mg/day.

2. It would appear from this particular study that dichlorvos in the amount of 1.5 mg/day (the level just below the minimal incipient toxicity) when fed daily over a 60-day period would also produce a significant depression in plasma cholinesterase which leveled off between 13 and 24% of normal.

3. In none of the studies was there any significant depression of RBC cholinesterase.

4. There were no significant changes in the CBCs, urinalyses, or liver-function tests except for a slight depression in hemoglobin in-four patients in Group E; probably due to the removal of blood over a long period of time.

5. There were no significant or serious side effects attributed to the administration of dichlorvos.

EPA Comment: This study was by the oral route, possibly relevant for the drug exposure studies.

22. CITATION: Slomka, M.B., and C. H. Hine. (1981). Clinical pharmacology of dichlorvos.

Acta Pharmacol. Et Toxicol 49:105-108.

Study Abstract: Polyvinyl resin formulation pellets (V-3 and V-12) containing dichlorvos were administered to male volunteers in single doses up to 32 mg/kg and repeated doses up to 16 mg/kg/day for up to three weeks. The cholinesterase activity depressions following single doses were dose related. Following multiple doses, the plasma cholinesterase activity was maximally depressed at all dose levels and the RBC cholinesterase activity depression was dose related.

EPA Comment: This study was the oral use of Dichlorvos as a drug, an antihelmetic, FDA approved use.

Additional information regarding the time course for achieving steady state after repeated exposure to dichlorvos.

23. CITATION: Boyer, A.C. (1975). Inhibition of Human Plasma Cholinesterase by Steady-State Concentration of Dichlorvos. Technical Progress Report No. M-44-75. July, 1975.

Study Abstract: The first order rate constant for the metabolism of dichlorvos by human blood plasma was determined. The constant was used to calculate the rate of dichlorvos infusion required to maintain an in vitro steady-state concentration of dichlorvos in plasma. The inhibition of plasma cholinesterase at various steady-state concentrations of dichlorvos was determined. The inhibition does not follow pseudo- first -order kinetics due to the dephosphorylation of the dimethylphosphorylated enzyme. However, the dephosphorylation reaction does follow first-order kinetics.

EPA Comment: Pharmacokinetic study, does not add anything additional to the database.

24. CITATION: Coulston, F., and T. Griffin. (1977). Cholinesterase Activity and Neuromuscular Function of Rhesus Monkeys Exposed to DDVP Vapors. Document prepared by Institute of Comparative and Human Toxicology, Albany Medical College, Albany, NY and the International Center of Environmental Safety, Albany Medical College, Holloman AFB, NM.

Study Summary: Male and female rhesus monkeys were exposed to dichlorvos (DDVP) vapors at a concentration of 0.051 μg/l for three months. During the investigation, observations of appearance and behavior were made and studies were conducted to determine effects on hematology, clinical chemistry (including plasma and erythrocyte cholinesterase activity) and neuromuscular function.

No effects of exposure to DDVP were observed in the appearance or behavior of the animals.

Routine hematology and clinical chemistry profiles remained within normal limits. Slight reductions in plasma cholinesterase activities (72% of pre-exposure values) and erythrocyte cholinesterase activities (64% of pre-exposure values) were observed.

A system utilizing surface electrodes was developed for obtaining reproducible measurements of maximum conduction velocities of the ulnar nerve and evoked action potentials of the flexor carpal ulnarus muscle. No effects on either parameter were observed during the three-month exposure period.

EPA Comment: THIS IS A DRAFT DOCUMENT. In monkeys there was a slight decrease in ChE activity.

25. CITATION: Hass, D.K., J.A. Collins, and J.K. Kodama. (1972). Effects of orally administered dichlorvos in Rhesus monkeys. JA. V MA. 161(6):714-719.

Study Summary: Thirty-two rhesus monkeys were treated with pelleted polyvinyl chloride resin formulations of dichlorvos at dosages ranging from 5 to 80 mg/kg daily or 8 and 20 mg/kg twice daily for 10 to 21 consecutive days. Twenty four of these monkeys were parasitized with Schistosoma mansoni. None of the monkeys developed clinical signs sufficiently emphatic to suggest organophosphate intoxication during the treatment period. Plasma and erythrocyte cholinesterase activities were significantly inhibited in all of the dichlorvos-treated monkeys.

EPA Comment: This study was the oral use of Dichlorvos as a drug, an antihelmetic, a FDA approved use.

Exposure Studies

Residential Pest-Strips:

26. CITATION: Batth, Scrat S., J. Singh, and D.C. Villeneuve. (1973). Dichlorvos vaporizers: method for evaluation under simulated household use. J Econ. Entom. 66(l):146-150.

Study Abstract: The room-sized chamber developed for evaluating dichlorvos vaporizers adequately simulated the practical home conditions, since levels or air-borne dichlorvos concentrations were found about the same both in the chamber and a house bedroom, each containing a typical dichlorvos vaporizer hung from the ceilings. Almost 100% kill of the susceptible laboratory house flies, *Musca domestica I.*, occurred in about 70 minutes when they were exposed in cages to an air-borne dichlorvos concentration of 0.1 μg per liter in the chamber whereas when exposed as free-flying insects, comparable mortality occurred in 45 minutes. No adverse effect on plasma cholinesterase was observed in rats exposed in the chamber to a dichlorvos vapor concentration of 0.5 μg per liter for 3 weeks.

EPA Comment: There was no effects in rats exposed to five time normal levels for 3 weeks. The NOAEL for inhalation exposure (acute and short term) would be 0.5 μg per liter for 3 weeks.

27. CITATION: Collins, R.D., and D.M. DeVries. (1970). Determination of Vapona Insecticide in Air and Food From Homes Treated with No-Pest Insecticide Strips. Shell Development Company. Technical Progress Report No. M-104-70, August, 1970.

Study Abstract: Shell NO-PEST® Insecticide Strips have been registered in the United States for use in the home at one strip per 1000 cubic feet for over five years. However, surveys have shown that the average user only purchases between two and three strips per season. Since data were not available for this type of use, an experimental trial was initiated to secure such information. Three or four strips were installed in fifteen typical Modesto homes. Air samples were taken over a 91-day test period. Breakfast and dinner samples were also taken at the same time intervals to correlate, if possible, air concentrations with food residues. Air concentrations were dependent upon the number of strips per unit volume and the amount of ventilation. The calculated daily residue value from the breakfast and dinner data showed a maximum of 0.03 ppm VAPONAP Insecticide one day after installation of the strips. These residue levels dropped to < 0.02 ppm 28 days after the start of the test. Fly control was generally satisfactory with rate of kill being related to the number of strips per unit volume and the amount of ventilation.

EPA Comment: This is an air residue study.